A STUDY OF THE CELLULAR PATHOLOGY OF CARCINOMA.

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It is not the intention of the writer, in the following paper, to enter at all into a general discussion as to the etiology of cancer. To do so, in the present state of our knowledge, would be simply to theorise, to indulge in useless speculation, adding rather to the mist of obscurity that enshrouds the origin of these growths than being of any practical or suggestive value.

This mist of obscurity, however, it may be said, is no denser, the veil no thicker than that which up to a comparatively recent period enveloped a number of the diseases with which mankind is afflicted, diseases which we now know to depend upon the presence of a specific organism. One after another of these so-called "microbic affections" have yielded, in so far as the causative agent is concerned, to the careful, patient investigations of the pathologist. There are still many, however, that remain refractory, refusing as it were to disclose the secret of their birth; and among them, overshadowing all perhaps, in the matter of importance to human kind is the one now under consideration—carcinoma.

The genesis of cancer is no longer in doubt; the studies of Waldeyer and of Thiersch having demonstrated almost beyond the possibility of question that it involves that of epithelium generally. Aimless, purposeless, destructive growths then, the proliferative and infiltrating elements of which are epithelial cells—cells always derived from preëxisting epithelium, standing invariably in a direct genetic relation to tissues originating in the epiblastic or hypoblastic layers of the blastoderm.

In so far as this, our knowledge of the pathology of cancer may be said to be accurate ; but here it practically ends. The question now is, and the answer is all important : What furnishes the stimulus for this aimless, infiltrative growth of epithelial elements ? What causes these tissue cells to leave their normal situation and by a process of excessive multiplication and proliferation not only to force their way into the lymph-spaces of adjacent structures, but to reproduce themselves in even remote parts of the organism ?

Theories without number have from time to time been advanced, our works on pathological science teeming with them, admitting, the while, that they are but theories. Thus long-continued mechanical irritation has been assigned as a cause ;—the failure of an organ, like the female breast, to perform its physiological functions;—developmental faults, as the aberrant embryonic remains of Cohnheim ;—errors in nutrition dependent on trophic neuroses ;—loss of balance, in after-life, between the connective and epithelial tissues, with insubordination of the latter (Thiersch) ; all of these and a host of others have been assigned a place among the etiological factors, and in a certain way, perhaps, they may all be entitled to such a place. For example, long-continued mechanical irritation is unquestionably, in very many cases, associated with cancer ; as witness the often quoted scrotal cancer of the sweeps, the arm of the paraffin worker and the cancer of the lip in smokers of clay pipes. In thousands of such cases, however, of prolonged irritation no cancer appears, and, *per contra*, in hosts of cases of cancer no history of such irritation can be obtained.

In view of these last considerations, we are certainly justified, for the present at least, in holding to the opinion of Cohnheim; that while most if not all of the factors mentioned have a place in the pathology of carcinoma, they tend rather to produce a constitutional, or it may be a local predisposition to the disease than to act, *per se*, as primary or proliferative causes ; that a certain weakening or diminution of the normal physiological resistance of the tissues is produced,

whereby morbid influences, at other times wholly inoperative, are enabled to produce their characteristic effects.

Billroth rather aptly defines this vague "predisposition" as a "specific formative irritability" of the tissues; while the acting morbid influence is referred to as a "specific formative stimulus." Adopting, then, Billroth's terminology (*The Mutual Action of the Living Animal and Vegetable Cell. New Sydenham Soc.*, 1894,) as the more explicit of the two, it would seem as though we are warranted, as has been said, in considering that the various forms of irritation, *et al.*, act by producing a "specific formative irritability" rather than as "specific formative stimuli." And yet for the production in various and varied situations of neoplastic formations as specific and unvarying in type as cancer, there must exist a form of stimulus, and a far-reaching and a continuously-acting stimulus that cannot be considered as otherwise than specific.

There are some features that characterise the growth of a carcinomatous tumor that seem to point to an analogy between them and certain other tumor formations that were some years ago classed by Virchow as "infective granulomata." Thus, that which was said by Dr. Green of a tuberculous deposit may with slight modification be equally well said of a cancer nodule: "The progressive character of the growth and its tendency to infect adjacent and distant portions of the body show the existence of some irritant capable of multiplying in the body and of spreading from primary to secondary foci."—Green, *Pathology and Morbid Anatomy. Seventh Am. ed., p. 554.*

This resemblance to a tuberculous process, this tendency to spread from primary to secondary foci, taken in connection with the characteristic cachexia that marks the progress of a carcinomatous growth, has led to the belief, now more or less widely spread, that cancer itself is of an infectious nature, even though its inoculability from man to man be not absolutely proven. Add to these features a certain observed tendency to hereditary transmission, if not of the disease itself, to at least a predisposition to the disease, and it is lit-

tle to be wondered at that the belief in an infective or parasitic origin should have become, in the minds of some pathologists at least, quite firmly implanted.

This idea having taken root, it is hardly necessary to state that a most active search for the infective agent has for a number of years been carried on ; with results that are certainly interesting, not to say startling, even while they astonish one by their variety.

Inasmuch as this paper has to do with some of the appearances that in a measure give color to this theory of parasitism in cancer, it may be well to state here that the bibliography upon the subject is already enormous ; so much so that any extensive reference to it is unnecessary and in a limited space impossible. With the exception, then, of a few casual allusions, the writer will content himself with a more or less imperfect demonstration of what may be found here at home in specimens of cancer met with in ordinary routine work.

In 1888, it will be remembered that Neisser, of gonococcus fame, published an elaborate paper embodying the results of his investigations into this subject, and placing the "parasite," which he described, in the *Coccidia* group of the Sporozoa. (*Vierteljahrschrift für Dermatologie und Syphilis*, 1888.) A little later (*British Medical Journal*, December 13, 1890,) Dr. W. E. Russell, of the Royal Infirmary, Edinburgh, described and depicted a so-called parasitic organism, presenting the appearance of round, homogeneous bodies, staining deeply with basic fuchsin and retaining it strongly when treated with other reagents, such as iodine-green. These he denominated "fuchsin bodies," considering them of a fungoid nature.

Contemporaneously with these, and continuing up to the present time, a host of other observers have described microscopic appearances attributed to result from the presence of an organism ; some considering it to be a Fungus or Alga, others a Protozoon. Thus, Soudakewitch, Pio Foà, Thoma, Metchnikoff, Korotneff, G. Sims Woodhead, Ruffer, in conjunction with Walker and Plimmer, C. H. Castle and a host

of others have, from time to time, described appearances that, whether dependent upon the presence of a parasite or not, demand, from the very importance of the subject, the closest study on the part of every student of pathology.

The assumption, on the part of these observers, that we are dealing with a parasitic organism, has, as is to be expected, met with a storm of criticism from pathologists of the highest repute. Thus, Klebs, Cornil, and, in our own country, Welch, of Johns Hopkins University, Prudden, of New York, and others, while admitting the appearances question the probability of their being due to a parasite, and ascribe them to various sources, to which we will refer later. Looking, however, at the matter from both points of view, weighing the evidence as we get it from the literature, *pro* and *con*, and it becomes at once manifest that we are not by any means justified in taking too radical a stand upon this subject; that there must be something to warrant the opinion of such men as Pio Foà, Thoma, Russell, Ruffer and G. Sims Woodhead, and, such being the case, careful and systematic study is the course that should be pursued, rather than the maintenance of a position of sceptical inactivity.

The feature that strikes one most forcibly, on looking over the various articles upon this subject, is the lack of uniformity in the results obtained. And it is this very feature perhaps that more than any other leads conservative minds to maintain a sceptical attitude, and it was this feature that led, in part, to the series of investigations that form the basis of this article; one of the objects having been to ascertain what there was in the microscopic appearances of cancer that should lead Dr. Russell to describe a round, homogeneous "fuchsin body" as a Fungus, while Neisser described a Protozoon; albeit the boundary line between the two is by no means well defined.

In addition to this, the writer, in making these investigations, hoped to be able to satisfy at least himself as to the following points:

1. Whether in the specimens of cancer met with in ordi-

nary class-room and routine work, without special methods of hardening and fixing, microscopical appearances could be found that might be interpreted as indicating the presence of an organism or body foreign to the tissues.

2. Whether these appearances are to be demonstrated in *all* specimens of carcinoma.

3. Whether they are peculiar to the carcinomata alone.

The possibility of being able to definitely determine the nature of these bodies was also considered, but it must be admitted, scarcely hoped for.

In selecting the material for these studies it will suffice to say that, with a few exceptions, it was taken from the ordinary material provided for laboratory work in the Medical Department of Yale University, under the supervision of Professor M. C. White. A few specimens, however, were personally prepared by the writer from tissues derived from various sources.

As to methods of fixing and hardening, they were various; chiefly, however, a simple passing of the tissues through alcohols of progressive strengths ; as, for example, 55 per cent, 67 per cent., 75 per cent., 82 per cent. and finally into 95 per cent., in which the specimens were kept. One or two specimens, involving nervous tissues, were hardened in "Müller's fluid, while one or two were fixed in a saturated solution of corrosive mercuric chloride for an hour, thence passing through progressive strengths of alcohol, as above. It will thus be seen that "especial methods of fixing and hardening" can hardly be said to be a predominant factor in the production of the appearances about to be described.

With regard to embedding and cutting of sections, all of the methods in common use were employed ; thus, some were embedded and cut in paraffin, some in celloidin and some were cut by the aid of the freezing microtome.

As to the methods of staining, a few words may well be said, although they will be made as few as possible.

Inasmuch as the first studies were devoted to the "fuchsin bodies" of Dr. Russell, the methods of staining employed

by him were naturally first made use of. He, it will be remembered, stained his sections first in a 2 per cent. solution of basic fuchsin in 5 per cent. carbolic acid; they were then placed in a 1 per cent. solution of iodine-green (Grübler's) which replaced the fuchsin in everything but the above mentioned bodies. (Op. cit.)

The writer soon found that practically the same or better results could be obtained with fuchsin and methylene-blue; there being no difficulty in demonstrating, in many sections of carcinoma, the rather characteristic, deeply stained, homogeneous bodies referred to. They vary in size from four to eleven or twelve micro-millimeters in diameter, and are met with singly, in twos, or threes, or in clumps of four or five lying both within the protoplasm of the cells and in the intercellular spaces. They are not confined, however, to the carcinomata for a section of lympho-sarcoma now at hand shows them in large numbers.

Not wishing at this time to devote much space to these bodies the writer would suggest, in taking leave of them, that they certainly merit close study. Red blood corpuscles readily take up and strongly retain basic fuchsin; and there are certainly in some of these "fuchsin bodies" appearances that suggest red corpuscles. There is, however, rarely so much variation in the size of the corpuscles, and they are almost never found within the cell protoplasm, although the writer has in one or two instances so found them.

Again the variation in the size of the "fuchsin bodies" serves as no real basis of distinction. As is well known we may have in certain pathological conditions the greatest diversity in the size and appearance of the red corpuscles. Thus in chlorotic conditions and pernicious anemia the so-called *microcytes* and *macrocytes*, as well as the huge "giganto-blasts" of Eichhorst, twenty micro-millimeters in diameter, are of frequent occurrence. For all this the writer, after careful study, is not disposed, for many reasons, to regard these "fuchsin bodies" as red blood corpuscles; their precise nature, however, it is impossible at present to state.

While still engaged in the study of these bodies, with other reagents than methylene-blue and fuchsin, certain appearances presented themselves from time to time, in some sections of carcinoma, that were not explainable by ordinary methods of reasoning. For instance in staining with such combinations as hematoxylin and safranine, hematoxylin and acid fuchsin, and hematoxylin and eosin there appeared to be certain enclosures in some of the larger epithelial elements that differed in appearance from the cell nuclei, and also from the bodies previously described ; and yet the differentiation was not sufficiently well marked, both nuclei and enclosures staining with hematoxylin, to warrant an expression of opinion as to their nature.

Without going too much into detail it will suffice to say that in the attempt to further differentiate these enclosures there was no staining reagent, or combination of stains in common use, but that was made use of, with, however, but indifferent success. At length attention was directed to an article or paragraph in Landois' Physiology (4th ed., p. 389,) on the beautiful results to be obtained in the demonstration of the nuclear figures that appear during the process of mitotic or indirect cell division (karyokinesis) by the use of a reagent now widely known as the "Ehrlich-Biondi" triple stain.

A trial of this reagent soon showed that by its use the enclosures mentioned above, the cell nuclei, and in fact, all of the component parts of the tissues could be differentiated with almost diagrammatic effect.

This "Ehrlich-Biondi fluid," as it was formerly called, owes its introduction really to Haidenhain ; and is a mixture of methyl-green, methyl-orange or orange G. (Grübler), and acid fuchsin ; (Rubin S. "saure fuchsin"). It is prepared by Grübler in a dry form ready mixed for use, 100 cubic centimeters of a 0.4 per cent. solution, with the addition of 7 cubic centimeters of a 0.5 per cent. solution of acid fuchsin (both aqueous) making the ordinary desk reagent. The method of using is given in nearly every recent work on histology.

Staining with this reagent *secundem artem*, using thin sections, cut in paraffin and with careful attention to technique we are told to expect the following results: the nuclei to appear of a bright green, the cell protoplasm taking an orange red or a reddish orange, while the connective tissues appear of the vivid or crimson red of the fuchsin.

Briefly, while we expect these results we don't always get them. At the best the stain is an uncertain one, acting at times and with certain tissues in a most inexplicable way. In this the experience of the writer coincides, I think, with that of most microscopists. At the same time, with all its uncertainties, it is a most invaluable aid in histological studies; a well stained section presenting a beautiful picture, and one that as has been said is almost diagrammatic.

Attention may be called to the fact that certain methods of hardening are not compatible with the use of this stain; thus in sections hardened in "Müller's fluid" the cell nuclei appear of a peculiar blue color, while the protoplasm appears of a rosy red, lacking, however, entirely in orange. Again embedding in paraffin seems to produce the only perfect results, inasmuch as sections cut in celloidin rarely show any orange in the protoplasm, unless it be after excessively long exposure to the stain. Embedding in paraffin, however, in itself leaves, in many cases, much to be desired. In tissues particularly of an encephaloid or purely cellular type, a marked and detrimental shrinkage is sure to take place. With celloidin this does not occur; and in such tissues it is vastly to be preferred. The slight differences in staining incurred by its use, are after all but differences of degree; and to one at all practised in histological work in no way impair the usefulness of either the reagent or method of embedding.

Returning now to the enclosures that have been referred to as occurring in certain of the epithelial cells of some sections of cancer, we may consider the appearances produced by the use of this "Biondi" reagent.

These, in the main, do not differ from those above

described ; but there appear in many of the cells, bodies that stain differently, and in other ways present an appearance entirely unique.

These enclosures appear to be of two kinds. Thus some of them appear to possess a distinct capsule or wall of a vivid red color, a protoplasm that remains colorless and a small distinct nucleus either centrally or laterally placed and which is also of a bright red. They are almost invariably contained within the cell protoplasm, it being very unusual to find them extra-cellular in position. They are found singly, in groups of two and three, or more, while in some cases the cell appears crowded with them, the nucleus being displaced or, as occurred in one instance, having entirely disappeared. In size they vary from scarcely more than two or three micro-millimeters in diameter up to twelve, or possibly fifteen or even more.

The other form presents an appearance entirely distinctive from this. In the first place they are never so small, rarely falling below twelve micro-millimeters in diameter. They are also perfectly spherical, have a small distinct nucleus, but the protoplasm stains most decidedly ; appearing of an indescribable lilac color, or of even a distinct bluish red ; the nucleus itself being of a more decided red. They are rarely found otherwise than one in a cell, although two cells containing them may be closely approximated. They never appear in groups.

Reference to the accompanying plates will give a better idea of these enclosures than could be obtained from pages of text.

The sections from which these drawings were made were taken from perhaps six or eight selected specimens of carcinoma, including both primary and secondary growths. All of these, I think, with one exception, were removed by Professor W. H. Carmalt, at the New Haven hospital, during the past year. This exception, and the one most prolific in the matter of "enclosures," was a secondary growth of an "encephaloid," or purely cellular type, involving the cere-

bellum and resulting in death. The primary growth was a scirrhus cancer (fibro-carcinoma) of the breast, which was also removed by Professor Carmalt some two years before.

The results embodied in these plates, with the brief appended description, may be said to be the results of something more than a year's study into the microscopical appearances of the carcinomata. Sarcomatous tissues have also come in for their share of study, with results that, while of great interest, are as yet too imperfect to warrant a consideration of them at this time, even if space permitted.

As to the "cancer bodies," or enclosures, the writer simply presents them as evidence corroborative of the results obtained by other pathologists. As will be noted, they correspond, except in minor details dependent in part upon a difference in "technique" in preparation, to the bodies described by, at least, Ruffer and Pio Foà. The results obtained by other observers are strangely at variance, and, it must be admitted, unexplainably so.

For a discussion, *pro* and *con*, as to the nature of these bodies, it is sufficient to refer to *Sajous' Annual of the Universal Medical Sciences* for 1895.

With regard to Cornil's idea that they are simply invaginated cells, it is hardly to be thought of when we refer to the examples of this depicted in Plate I., Figs. 4, 5 and 6, and Plate III., Fig. 24. Dr. Welch, of Johns Hopkins, in expressing the opinion* that they are fragments of eleidin or keratohyalin, or other products of protoplasmic degeneration, is probably in error. If such were the case, fragments of eleidin or kerato-hyalin, under similar treatment, would present the same appearances *in normal tissues*, and the same may be said regarding other explanations that have from time to time been offered.

A process of endogenous cell formation has been suggested as explanatory of these appearances; but here again comes in "control sections" of other instances of exceedingly rapid cell proliferation, such as granulation tissue and certain forms

* Quoted by Dr. Ruffer, *Jour Path and Bact.*, 1893.

of rapidly growing adenomata. Such appearances, arising from endogenous cell formation, or any other method of cell formation are not, and, so far as the writer's knowledge goes, never have been demonstrated in these or other tissues.

Mastzellen, the so-called "feeding cells" of Altman, have also been mentioned in this connection, for no other reason that the writer can see than that certain of the Protozoa in their early stages present the appearance of a simple mass of granular protoplasm. These *Mastzellen* are very abundant in certain rapidly growing tissues, as, for instance, in young animals, such as the sheep, where they may be readily demonstrated in the lung. They are also met with very frequently in the human subject, and are particularly noticeable in some sarcomata.*

Professor Klebs, in June, 1890, refers to these enclosures as hyaline bodies, and is "decidedly disposed to regard them as degenerative products" (*Deutsche Medicinische Wochenschrift*, Nos. 24, 25, 32, June, 1890). Without, however, going into the discussion further, it may be said that the foregoing sum up the most rational attempts at explanation of these appearances, aside from those in which they are regarded as Protozoa.

In so far as the writer's experience goes, these enclosures, *as above described*, are peculiar to the carcinomata. Professor M. C. White states that he has met with one or more in a section of apparently normal kidney. The writer, however, had no opportunity of examining it. A. A. Kanthack says (*British Medical Journal*, March 14, 1891,): "These organisms, whether we call them Protozoa, or psorospermiæ, or sporocysts, or what not, occur, and even frequently, in other diseases, even in apparently healthy tissues." Be this as it may, the study by the writer of over a thousand sections of various tissues has failed to show them in any other situation.

As to their occurrence in *all* carcinomata as much can not be said. Some sections have failed to show them, but sec-

* See Plate I., Fig. 9.

tions from another portion of the tumor, possibly, might have done so. In the vast majority of instances, however, they are to be found without great difficulty. They are more abundant, seemingly, in soft, rapidly growing cancers, as for instance, the encephaloid growth above referred to. They are also more readily demonstrated, apparently, in secondary growths, although this cannot be said to be invariable. They cannot be said to be everywhere present, or, as a rule, abundant. One may have quite a search without finding a single enclosure, while again a solitary field may show half a dozen or more. As has been said, they are almost invariably contained within the protoplasm of the cell. The writer has never found one within the cell-nucleus, and in but one or two instances have they appeared outside the cell.

A short time since, the writer was enabled, through the courtesy of Dr. Charles J. Foote, to see the colored plates, together with original paper, of Ruffer and Walker (*Jour. of Path. and Bact.*, 1893). Engravings, however, prepared from these, appear in Green's *Pathology* and *Morbid Anatomy* (Seventh Am. Ed.).

Dr. Ruffer employed the "Ehrlich-Biondi" stain with good effect, describing, however, an orange cell protoplasm with a parasite (?) of "Cambridge" blue. Precisely his effects the writer has been unable to obtain, but it is to be noted that he embedded and cut in paraffin, while the drawings that accompany this paper were from tissues cut in celloidin. Again, Dr. Ruffer describes the parasite as refractory to hematoxylin, while Pio Foà (*Annual Universal Medical Sciences*, 1894,) demonstrated his bodies most satisfactorily by its use. The writer finds, with him, that they stain very readily with ripe hematoxylin (Gage's), but inasmuch as the cell nuclei do the same, it requires a practised eye to differentiate them.

We have thus, in a necessarily brief and incomplete way, studied some of the appearances that, as has been said, in a measure tend to give color to the theory that cancer is dependent upon the presence and growth of a specific organ-

ism; and we have also considered, in part, the various explanations that have from time to time been offered to account for these appearances. Most, if not all, of these attempts at explanation, however, are manifestly inadequate and by no means cover the entire ground, and hence it is useless, in the face of such a mass of evidence as has accumulated, to attempt to deny that the cells of carcinoma, in many cases, contain structures that, if we can rely upon our present teachings in the science of histology, are not an integral portion of the tissues. At the same time, however, we are forced to admit that evidence as to their precise nature is wholly and entirely wanting. And this must be so, inasmuch as at present we are dependent upon mere morphological appearances for our knowledge, rather than upon biological detail, and a knowledge of the life history of the organism, if organism it be. Artificial cultures have been attempted, but up to the present time have not been successful. We are hence compelled, as it were, to suspend judgment, bending our energies meanwhile to the development of thorough and systematic methods of study, methods which involve the study of the living, growing cancer, rather than that of simple microscopic sections alone.

The fact has been before referred to that Neisser (*loc. cit.*) was among the first to regard these structures as Protozoa (class Sporozoa, sub-class Coccidia). In this he is supported by nearly all of the recent observers, including that most accurate of zoologists, Metchnikoff. Even the great Billroth inclines to the same belief (*op. cit.*). He was apparently much impressed by the investigations of Bollinger and J. Pfeiffer into the etiology and pathogenesis of the infectious epithelioma of birds; they stating as follows: "The epithelioma formation is brought about by the immigration of the germs of a Protozoon of the class of the Sporozoa (*Gregarinæ*) into the cells of the *rete malpighii*. Whilst the cells affected by the parasite are entirely consumed up to a narrow border line, and the nucleus pressed against the cell wall, a proliferation of the still intact epithelial cells in the neighborhood of

the invaded region takes place, the progeny of which are successfully invaded by the parasite."

The simple comparison of this description with some of the appearances in the accompanying drawings* in itself furnishes some food for thought.

For the best brief exposition of the life history of the Protozoa themselves, the reader, perhaps, had better refer to Lankester's article in the *Encyclopedia Brittanica*. A few words, however, based upon his terminology may perhaps be offered as a fitting conclusion to this paper.

"Protozoa," as is well known, is the name applied to the lowest grade of the animal kingdom, being sharply and definitely distinguished from the higher groups of Metazoa and Enterozoa by the fact that they are structurally single cells or units of protoplasm ; whereas the latter consist of aggregations of such units, which are embryonically arranged into two, or in the highest types, three layers. While, however, the Protozoa are essentially unicellular organisms, this is by no means always the case ; as many consist of aggregations of such cells with, however, this marked and peculiar distinction, there is no differentiation into embryonic layers, and each component cell is capable at any time of taking up and maintaining an *independent existence*, the cohesion between the cells having no economic significance.

As distinguishing the Protozoa from the lower grades of plant life—the Fungi and Algæ—we have the one great feature that marks plant life as distinguished from animal life in the higher orders ; the plants are synthetical, capable of elaborating their nourishment from the simplest compounds, as carbonic acid and ammonia, while the Protozoa, like other animals, require the preformed, higher organic compounds for their nutrition. (The somewhat anomalous position of some of the Fungi it is unnecessary to discuss here.)

The Protozoon individual, then, is a simple mass of protoplasm, varing in diameter from $\frac{1}{1000}$ of an inch up to an inch (as witness the gigantic *Nummulites*). In common with

* Plates II. and III.

other forms of animal life, they are endowed with the power of motion, possess a certain irritability, and are capable of growth and reproduction. Perhaps not their least important characteristic, when considered in connection with cancer, is that of "producing by chemical processes that take place in their substance (over and above those merely related to nutrition) a variety of distinct chemical compounds, which may form a deposit in or beyond the superficial protoplasm of the

FIG. 28.
Cyst of *Klossia helicina*.

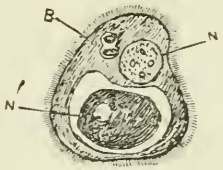

FIG. 29.

Renal cell, from *Helix hortensis*, containing full grown Gregarine, *Klossia helicina*, (copied from Lankester). Compare with Figs. 16, 17, 18 and 26. *N*. Cell nucleus. *N'*. Body, nature unknown. *B*. Nucleus of *Klossia*.

corpuscle, or may accumulate centrally." It will be noted that there is every possibility of these chemical products producing analogous effects to the so-called "toxines" of the pathogenic bacteria.

As to modes of growth and reproduction, the Protozoon follows the same course as tissue cells in general. While simple binary division is the rule, it is very usual that under given conditions the Protozoon breaks up rapidly in from ten to a hundred little pieces, each of which leads an independent life and grows to the form and size of its parent. This is shown in Fig. 28, where the Protozoon has gone on to the

formation of a cyst, the contents of which break up into a number of *chlamydospores* (coated spores). The analogy to Figs. 15 and 23 is very striking.

A discussion as to the part played by various Protozoa in the life drama of both vertebrates and invertebrates, while of exceeding interest, is impossible at this time. As is well known, they are intimately associated in the human family with Paget's disease of the nipple, with the so-called *Keratosis follicularis*," and with *Molluscum contagiosum*." The often quoted *Coccidium oviforme*, that so frequently occurs in the liver of the rabbit, particularly of those that inhabit marshy districts, not infrequently gains access to and excites inflammatory processes in the human liver. The so-called "Rainey's tubes," or "sacs of Meischer," that occur in the striated muscle fibers of the hog (*Sus scrofa*), are simply the chlamydospore cysts of a Protozoon, in the majority of cases being filled with falciform young. The epithelioma of birds we have already referred to. Finally, as we pass down the animal scale, the gills of the fresh water perch, the common earth-worm, the garden snail and the familiar cockroach (*Blatta orientalis*) are all of them fertile fields for the demonstration of Protozoa.

These instances, together with innumerable others that might be cited, simply show the extent to which these lowly organisms participate in pathological as well as apparently non-pathological processes occurring in the various types of animal life.

In concluding, the writer once more begs to call attention to the fact that the foregoing demonstration of the cell-enclosures of cancer simply corroborates the results obtained by a number of pathologists during the past hemidecade. In no sense do they furnish indubitable evidence that the disease is dependent upon the presence of a parasite. Neither can there be said to exist even proof positive that these bodies are Protozoa. The resemblance, however, of the anatomical details here presented, to those that illustrate the various phases in the life history of certain of these

organisms, is certainly very striking. Still, the evidence is far from complete, and for the present we are simply justified in considering the whole matter as *sub judice*. In the face, however, of the facts presented, we can certainly do no less than admit that the cells of carcinoma, in very many instances, present appearances that are wholly and entirely unexplainable by any reasoning based upon our present knowledge of pathological histology.

The writer wishes, in closing, to acknowledge his great indebtedness to Dr. M. C. White, Professor of Pathology in Yale University, for the advice and assistance so kindly and courteously given.

PLATE I.

Fig. 1. Cancer cells.
n. Nuclei.
s. Small round cells.

Fig. 2. Cancer cell.
Nucleus dividing.

Fig. 3. Cancer cell.
Two nuclei.

Fig. 4. Cancer cells.
Invaginated. *n*. Nuclei.

Fig. 5. Cancer cells.
Invaginated.

Fig 6. Cancer cells.
Division after invagination.

Fig. 7. Cancer cell.
Hydrophic degeneration about nucleus (*n*).

Fig. 8. Cancer cells.
Invaginated cell; nucleus broken up.

Fig. 9. Mast Zellen. (Methyl-blue.)

Zeiss. Objective, $\frac{1}{12}$. Oil immersion. Ocular, 4. C. W. K., Pinx.

Plate I

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Fig 1

Fig 2

Fig 3

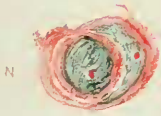

Fig 4

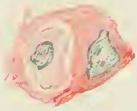

Fig 5

Fig 6

Fig 7

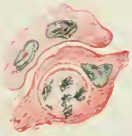

Fig 8

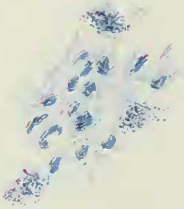

Fig 9

PLATE II.

Fig. 10. Cancer body or enclosure.
From scirrhus of breast.
n. Nucleus.

Fig. 11. Cancer body or enclosure.
(From another case.)

Fig. 12. Two cancer bodies in one cell.
(From scirrhus.)

Fig. 13. Three cancer bodies.
(From scirrhus of breast.)

Fig. 14. Five cancer bodies involving two cells.
From encephaloid of cerebellum.
v. Vacuole.

Fig. 15. A crowd of cancer bodies.
From same specimen as Fig. 14.

Fig. 16. Different type of enclosure.
From encephaloid.

Fig. 17. Different type of enclosure.
From same growth as in Fig. 16.

Fig. 18. Two enclosures involving two cells.
From same growth as in Figs. 16 and 17.

Zeiss. Objective, $\frac{1}{12}$. Oil immersion. Ocular, 4. C. W. K., Pinx.